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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/360,934	07/26/1999	ANTONELLO COVACCI	CHIR-0158	4878

27476 7590 06/20/2002

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EXAMINER	
BUI, PHUONG T	
ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 06/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/360,934	Covacci et al.
Examiner	**Art Unit**
Phuong Bui	1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 21, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *40 and 54-101* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *40, 54-65, 74-86, and 95-101* is/are rejected.

7) ☒ Claim(s) *66-73 and 87-94* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jul 26, 1999* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 26
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The Office acknowledges the receipt of the Interview Summary communication, Paper No. 24, filed October 2, 2001, the Information Disclosure Statement, Paper No. 25, filed January 18, 2002, and the Response and Amendment F, Paper No. 27, filed March 21, 2002. Claims 38, 39 and 42 have been cancelled. New claims 54-101 have been entered. Accordingly, claims 40 and 54-101 are pending and are examined in the instant application.

2. The previous indication of allowable subject matter is hereby withdrawn in view of the review and application of a new prior art set forth below. Any inconvenience this may cause Applicant is regretted.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

4. This application has been filed with informal drawings which are acceptable for examination purposes only. The Office no longer defers the filing of formal drawings. **Accordingly, formal drawings are required in response to this Office Action.**

Claim Objections

5. Claims 66, 69, 70, 87, 90 and 91 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must refer to other claims from which it depends in the alternative only. In this case, each of these claims depends from previous claims in

the cumulative form. See MPEP § 608.01(n). Accordingly, these claims and the claims that depend from them (claims 67, 68, 71-73, 88, 89 and 92-94) have not been further treated on the merits.

35 U.S.C. 112, second paragraph

6. Claims 55-62, 74-86 and 95-101 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Initially, the Office notes that Applicant now states the phrases "substantially no toxicity" and "substantially reduced toxicity" mean that the *H. pylori* cytotoxin (CT) polypeptides do not exhibit statistically significant cytotoxic effects, and would thus be acceptable for use in human vaccine. In the previous Office action, the Office stated that it understood these phrases to mean "does not exhibit statistically significant cytotoxic effects to a *H. pylori* host" and that cytotoxic effects mean the ability to cause vacuolation and cell death. It is not clear if Applicant's current "clarification" is adding the further requirement that these phrases imply that the claimed polypeptides are acceptable for use in human vaccines or whether Applicant is confirming the Office's previously stated understanding. Clarification of this matter is now required.

In claims 55, 58, 59, 76, 79 and 80, Applicant recites that the polypeptide further comprises a fragment or derivative of a *H. pylori* CT polypeptide. Several issues are raised by these claims. Since SEQ ID NO:3 is the amino acid sequence for the *H. pylori* CT polypeptide,

claims 40 and 74 are reciting polypeptides that are fragments of the *H. pylori* CT polypeptide. Accordingly, claims 55, 58, 59, 76, 79 and 80 are reciting that fragments of the *H. pylori* CT polypeptide further comprising fragments of the *H. pylori* CT polypeptide. This is not understood.

In claims 55, 57-59, 76 and 78-80, Applicant's recite that the polypeptide further comprises a "derivative" of a *H. pylori* CT polypeptide. The specification recites that the cytotoxin of *H. pylori* refers to the protein whose nucleotide sequence and amino acid sequences are shown in Figures 1 and 2, "and their derivatives" (specification page 5, lines 31-34). On page 7 of the specification, Applicant describes examples of proteins having conservative amino acid substitutions. However, these examples are not specific to "derivatives". The term "derivatives" therefore has not been defined in the specification. This term renders the claims indefinite in that it is not clear how much of the protein's original structure must be retained such the resulting protein would be considered to be a "derivative".

In claims 58 and 79, it is not clear what "immunologically identifiable with" is intended to mean as this phrase has not been defined in the specification. Is the polypeptide claimed supposed to react with at least one antibody raised to an epitope of the protein of SEQ ID NO:3 or is the claimed polypeptide immunologically indistinguishable from the protein of SEQ ID NO:3?

In claims 59 and 80, it is not clear which polypeptide, the claimed recombinant polypeptide or the *H. pylori* CT polypeptide, that "said polypeptide" is referring to on line 4.

Moreover, "the functional aspects" on line 4 lacks antecedent basis. What are these functional aspects and what is intended by "which do not substantially affect" mean?

In claim 74, Applicant recites that the claimed polypeptide is immunogenic. In the context of this claim, the Office assumes that the claimed polypeptide contains at least one epitope from SEQ ID NO:3.

In claim 84, Applicant recites a non-toxic polypeptide expressed from 15 contiguous nucleotides from SEQ ID NO:2. No functional recitation has been provided, nor has Applicant required that the polypeptide be expressed from 15 contiguous nucleotides of SEQ ID NO:2 that represent 5 in-frame codons. It does not appear that Applicant intended the claim to include polypeptides that are neither functional nor included within SEQ ID NO:3.

35 U.S.C. 112, first paragraph

7. Claims 55, 57-59, 61, 62, 76, 78-80, 82-86, 95 and 96 are rejected 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *H. pylori* cytotoxin SEQ ID NO:3, or the polypeptide encoded by the polynucleotide sequence of SEQ ID NO:2, and immunogenic fragments thereof, does not reasonably provide enablement for any polypeptide encoded by any 15 contiguous nucleotides of SEQ ID NO:2, or any derivative of any of the recited polypeptides, having substantially no toxicity.

The specification defines cytotoxin of *H. pylori* as the protein, and fragments thereof, whose nucléotide sequence and amino acid sequence are shown in Figs. 1 and 2, respectively, and

their derivatives, and whose molecular weight is about 140 kDa (p. 5). The specification also defines polypeptide as having an amino acid sequence identical to that of a polypeptide encoded in the sequence, or a portion thereof wherein the portion consists of at least 3-5 amino acids (p. 14). The claims also recite derivatives of the *H. pylori* cytotoxin and polypeptides expressed from any 15 or more contiguous nucleotides of SEQ ID NO:2. Based upon these definitions, the claimed polypeptide can be any 3-5 amino acids from any source, since it is unclear what properties are retained in the derivatives. Applicant should also note that the claimed polypeptide is "recombinantly produced" and does not require that the claimed polypeptide be isolated/purified from *H. pylori* cytotoxin. Similarly, claims 95 and 96, which comprise at least ten amino acids, are also not enabled since no SEQ ID NO. was cited and thus the claims read on any 10 or 15 amino acids from any source.

Assuming arguendo that the claims do not read on any protein from any source, but that the polypeptides are obtained from *H. pylori* cytotoxin, claim 74 is still not enabled because it does not require inducing of the production of antibodies specific to *H. pylori*. The specification discloses diagnostic and vaccine applications (p. 4). Vaccine applications are not enabled for reasons of record. Diagnostic applications minimally require an antigen-antibody interaction specific to *H. pylori* cytotoxin, which claim 74 does not require. It is unclear how one skilled in the art would be able to use any 10 amino acid sequence which is not specific to *H. pylori* cytotoxin and does not induce production of antibodies to *H. pylori* for diagnostic purposes or

any other well-established uses without undue experimentation. For example, the previously sent oligopeptide sequence search results disclose proteins having an eight consecutive amino acid match with various regions of Applicant's SEQ ID NO:3 which are not *H. pylori* cytotoxins. Thus, antibodies produced to any of these eight polypeptides would not be specific to *H. pylori*. Accordingly, Applicant has not enabled 3-5 amino acid polypeptides which do not induce the production of antibodies specific to *H. pylori* for any disclosed or well-established applications as commensurate in scope with the claims.

8. Claims 80, 84, 95 and 96 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Aside from the fact the claims broadly read on a protein of any size from any source, which Applicant is clearly not in possession of, the breadth of the claims also encompasses all *H. pylori* cytotoxin mutants and allelic variants. Applicant discloses the cytotoxin sequence from *H. pylori* strain CCUG 17874 (p. 48). There is insufficient relevant identifying characteristics from a single strain to allow one skilled in the art to predictably determine complete structures of other cytotoxin sequences from other *H. pylori* strains, or their mutants and allelic variants, absent further guidance. Since the claimed genus, i.e., CT (cytotoxin) polypeptides, encompasses undisclosed CT polypeptides from other species (strains) yet to be discovered, the disclosed

structural feature for one species (strain) does not constitute a substantial portion of the claimed genus. Therefore, the disclosure of a single cytotoxin sequence from a single strain of *H. pylori* does not provide an adequate description of the claimed genus, and in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that Applicant was in possession of the genus of CT polypeptides as claimed (see Written Description Requirement published in Federal Register/ Vol.66, No. 4/ Friday, January 5, 2001/ Notices; p. 1099-1111). It is suggested that Applicant recite SEQ ID NO:3 and that the fragments claimed can induce the production of antibodies to the *H. pylori* cytotoxin to obviate this rejection.

Claim Rejections - 35 USC § 102 and 103

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 40, 54-65, 74-86, and 95-101 are rejected under 35 U.S.C. 102(e) as being anticipated by, or alternatively, under 35 U.S.C. 103(a), as being unpatentable over Cover et al. (U.S. Patent No. 6,054,132).

Cover et al. teaches isolation and purification of the *H. pylori* cytotoxin, identified as an 87 kDa protein. The protein has a number of peptides that read on the various recited lengths of the claimed polypeptides including a 24 amino acid fragment reading on positions 34-56 of SEQ ID NO:3, a 14 amino acid fragment reading on positions 168-180 of SEQ ID NO:3 and an 8 amino acid fragment reading on positions 626-632. These fragments are each at least 5 amino acid residues in length and therefore, these sequences cover a polypeptide expressed from at least 15 contiguous nucleotides from SEQ ID NO:3. Moreover, the first and second sequences cover a polypeptide of at least 10 amino acids of SEQ ID NO:3 or a polypeptide expressed from at least 30 contiguous nucleotides from SEQ ID NO:2. Finally, the first sequence covers a polypeptide of at least 15 amino acids from SEQ ID NO:3 or a polypeptide expressed from at least 45 contiguous nucleotides from SEQ ID NO:2.

Cover has an effective filing date of February 26, 1992, which precedes Applicant's earliest priority date. In addition, Cover teaches that the protein or fragments thereof may be included in a vaccine preparation in toxoid or detoxified form (Cover, column 16, lines 43-46). Though Cover does not teach whether the fragments referred to above are themselves non-toxic, one skilled in the art would reasonably have expected them to be inherently non-toxic. The

vacuolizing activity of the *H. pylori* cytotoxin is taught in the prior art to likely involve at least a mechanism implicating ion-transport since the cytotoxin shares homology with various ion-transporting ATPases. Further, Cover teaches that numerous non-toxic epitopes exist in view of the significant differences between toxicity-neutralizing antisera titers versus ELISA antisera titers. When the Office finds a reasonable basis supporting the assertion that the prior art products and that claimed are the same, the burden shifts to Applicant to show that they are not. MPEP 2112, referring to *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Alternatively, even if the particular fragments disclosed by Cover are toxic, the production of non-toxic fragments of the Cover's *H. pylori* cytotoxin would have been obvious to one of ordinary skill in the art in view of the statements made in the declaration of Giuseppe Del Giudice, filed August 7, 2000 under 37 CFR 1.132. Therein, in paragraphs 9-12, declarant states that the identification of non-toxic fragments of the *H. pylori* cytotoxin was routine for those skilled in the art. Accordingly, one skilled in the art would have found it obvious to determine the non-toxic fragments of *H. pylori* cytotoxin, again especially in view of the fact that Cover recognized that there existed epitopes that did not contribute to the vacuolating activity of the toxin.

11. No claim is allowable.

12. Papers relating to this application may be submitted to Technology Sector 1 by facsimile transmission. Papers should be faxed to Crystal Mall 1, Art Unit 1638, using fax number (703) 308-4242. All Technology Sector 1 fax machines are available to receive transmissions 24

hrs/day, 7 days/wk. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Bui whose telephone number is (703) 305-1996. The Examiner can normally be reached Monday-Friday from 6:30 AM - 4:00 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Phuong Bui
Patent Examiner
Group Art Unit 1638
June 12, 2002

Phuong Bui

PHUONG T. BUI
PRIMARY EXAMINER